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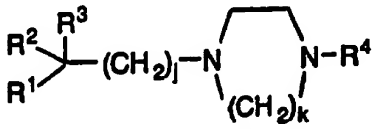
(54) Title: DIARYLALKYL CYCLIC DIAMINE DERIVATIVES AS CHEMOKINE RECEPTOR ANTAGONISTS

(57) Abstract

Cyclic diamines of formula (I) or their pharmacologically acceptable acid addition salts, and their medical applications are described. These compounds inhibit the action of chemokines such as MIP-1a and/or MCP-1 on target cells, and are useful as a therapeutic drug and/or preventative drug in diseases, such as atherosclerosis, rheumatoid arthritis, and the like where blood monocytes and lymphocytes infiltrate into tissues.



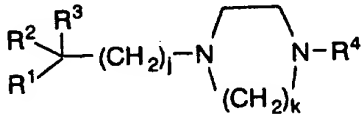
(I)

r is not 0 and A^3 is not a single bond or -CO-.

Furthermore, if R^3 represents a hydrogen atom and k represents 2, R^7 is not unsubstituted; m is not 0 and R^{11} is not a substituted or unsubstituted phenyl group.

If R^3 is a cyano group, R^7 is not unsubstituted, and the substituent groups for R^7 are not halogen atom, C_1-C_6 lower alkyl group or C_1-C_6 lower alkoxy group.]

The present invention provides a method of inhibiting the binding of chemokines to the receptor of a target cell and/or a method to inhibit its action onto a target cell using a pharmacological formulation containing as an active ingredient, a cyclic diamine derivative or its pharmacologically acceptable acid adduct (Invention 2) represented by the formula [II] below:



[II]

[wherein R^1 and R^2 are identical to or different from each other representing a phenyl group or an aromatic heterocyclic group having 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, and/or nitrogen atoms, in which the phenyl or aromatic heterocyclic group may be substituted by any number of halogen atoms, hydroxy groups, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, phenyl groups, benzyl groups, phenoxy groups, methylenedioxy groups, C_1-C_6 hydroxyalkyl groups, carboxy groups, C_2-C_7 alkoxycarbonyl groups, C_2-C_7 alkanoylamino groups, dioxolanyl grpoups, or by group represented by the formula: ~~NR^5R^6, or else may~~ be condensed with a benzene ring to form a condensed ring, furthermore above substituents for the phenyl or aromatic heterocyclic group and the condenced ring condenced with a benzene ring are optionally substituted by any ssubstituents independently selected from halogen atoms, hydroxy groups, or C_1-C_6 lower alkoxy groups, and R^5 and R^6 may be identical to or different from each other representing hydrogen atoms, C_1-C_6 lower alkyl groups, or C_2-C_6 lower alkenyl groups;

R^3 represents a hydrogen atom, hydroxy group, cyano group, C_1-C_6 lower alkoxy group or C_2-C_7 lower alkanoyloxy group;

j represents an integer of 0-3;

k represents 2 or 3;

R^4 is a group represented by :

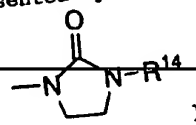
1) Formula: $-A^1-R^7$

(in the formula, R^7 represents a phenyl group which may be substituted by any number of the same or different {halogen atoms, hydroxy groups, amino groups, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, cyano groups, nitro groups, trifluoromethyl groups, C_2-C_7 alkoxycarbonyl groups, C_2-C_7 alkanoyl groups, C_1-C_6 alkylsulfonyl groups, trifluoromethylsulfonyl groups, phenylsulfonyl groups (which may be substituted with a hydroxy group), 1-pyrrolylsulfonyl groups, C_1-C_6 hydroxyalkylsulfonyl groups, C_1-C_6 alkanoylamino groups, or a group represented by the formula: $-CONR^8R^9$) in which R^8 and R^9, identical to or different from each other, represent hydrogen atoms or C_1-C_6 lower alkyl groups; A^1 is a group represented by the formula: $-(CH_2)_m-$ or a group represented by formula: $-(CH_2)_p-G-(CH_2)_q-$ in which G represents G^1 or G^2; G^1 represents -O-, -CO-, $-SO_2-$, -CO-O-, -CONH-, -NHCO-, -NHCONH-, or $-NH-SO_2-$; G^2 represents $-(C=NH)NH-SO_2-$, -CO-NH-NH-CO-, $-CO-NH-NH-CO-NR^{10}-$, $-CO-NH-CH_2-CO-$, $-CO-NH-NH-SO_2-$, or $-CO-N(CH_2-CO-OCH_3)-NH-CO-$; R^{10} represents a hydrogen atom or a phenyl group; m is an integer of 0-3; p is an integer of 1-3; q represents 0 or 1);

2) Formula: $-A^2-R^{11}$

(wherein A^2 represents -CO- or $-SO_2-$; R^{11} represents:

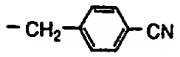
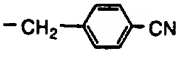
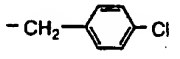
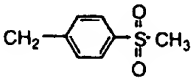
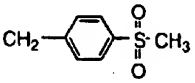
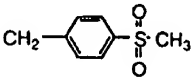
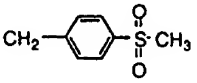
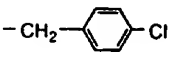
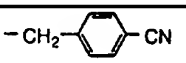
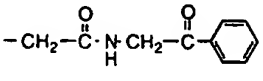
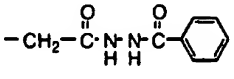
a) A phenyl group which may be substituted by any number of the same or different {halogen atoms, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, groups represented by formula $-CH_2-NR^{12}R^{13}$ or groups represented by the formula:



),

b) An aromatic monocyclic heterocyclic group having 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, and/or nitrogen atoms, and optionally substituted with any of the same or different number of {halogen atoms, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups), or

Table 1.1

Compound No.	R^1	R^2	R^3	j	k	R^4
1			CN	2	2	
2			CN	2	3	
3			CN	2	3	
4			CN	2	3	
5			H	0	3	
6			H	1	3	
7			H	2	2	
8			H	2	2	
9			H	2	2	
10			H	2	2	
11			H	2	2	
12			H	2	2